REMARKS

This Reply is responsive to the Office Action dated January 15, 2003. Entry of the amendments and remarks submitted herein and reconsideration of the claimed subject matter pursuant to 37 CFR §1.112 are respectfully requested.

I. Status of the Claims

Claims 1, 5 and 20-39 were pending in this application at the time of the Office Action dated January 15, 2003. Claims 1, 5, 20-31, 33, 35 and 39 were withdrawn from consideration. As a result of this amendment, no claims have been canceled. Accordingly, claims 32, 34 and 36-38 are now pending and under examination.

Applicants note that page 1 of the Office Action indicates that claims 32, 34 and 36-38 are rejected and claim 34 is objected to. It is not clear, however, from the remaining pages of the Office Action why claim 34 is objected to. Clarification is requested.

II. Amendments to the Specification and the Claims

Claim 36 was amended above to indicate that member (b) of the recited Markush group is a nucleotide primer capable of amplifying a nucleic acid encoding a protein comprising amino acids derived from SEQ ID NO: 4 comprising deletion, substitution or insertion of at least one amino acid, wherein said derived protein has cell-calcification inhibitory activity and increases DNA synthesizing ability of cells. Support for this amendment may be found in the specification at the very least at page 8, lines 9-13, and

page 22, lines 7-16. No prohibited new matter has been added by way of this amendment.

III. Rejection for Obviousness-Type Double Patenting

Claims 32 and 34 were rejected for obviousness-type double patenting over claims 1-2 of U.S. Patent 6,294,354. Applicants respectfully traverse the rejection. Pending claims 32 and 34 are directed to pharmaceutical compositions comprising an erg gene, or a C-11 or c-erg gene, respectively. Pharmaceutical compositions comprising DNA were found to be separately patentable from the DNA molecules themselves in the restriction requirement set forth on October 26, 1998, in U.S. Serial No. 08/878,177 (the application for US 6,294,354). Specifically, Group II was elected in S.N. 08/878,177 and this subject matter issued in US 6,294,354. In Group VIII, claims 16 and 18 are identical to pending claims 32 and 34. The present application is a divisional application of U.S. Serial No. 08/878,177. Therefore, an obviousness-type double patenting rejection is improper. See MPEP § 804.01. Reconsideration and withdrawal of the rejection are respectfully requested.

IV. Rejection under 35 U.S.C. §102

Claims 32 and 34 were rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Dhordain *et al* (1995). According to the Office Action, the erg gene composition of Dhordain appears to be indistinguishable from the pharmaceutical compositions of claims 32 and 34. Applicants respectfully traverse the rejection.

According to Dhordain *et al.*, the authors of that reference cloned the ck-erg (c-erg) gene to study its expression during chicken development (see the abstract). The clone was used to perform Northern blot studies on various chicken tissues, and *in situ* analyses were performed to show that the gene is expressed in mesoderm and ectoderm-derived tissues. There is no indication in Dhordain *et al.* that the cloned gene was formulated into or used as a pharmaceutical composition.

On page 6 of the Office Action, the Examiner stresses that the claims are drawn to pharmaceutical compositions comprising genes and as such, the claims "encompass the intended use of the claimed compositions in gene therapy." There is no mention in Dhordain regarding the use of the cloned erg gene in a pharmaceutical composition for gene therapy. If the intended use of the claimed composition is a limitation to be considered for purposes of enablement, then for consistency, it is also a limitation with regard to the prior art.

Given that a reference cited under §102 must teach every limitation of the claim and Dhordain *et al.* does not teach that the cloned erg gene may be used as a pharmaceutical as recited in claims 32 and 34, reconsideration and withdrawal of the rejection under §102(b) based on Dhordain *et al.* are respectfully requested.

V. Rejections under 35 U.S.C. §112, first paragraph

A. Enablement rejections

Claims 32 and 34 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way so as to enable one skilled in the art to make and use the invention. Essentially, the

Office Action notes that the claimed compositions are directed to pharmaceutical compositions comprising genes and that the claims therefore encompass the intended use of the claimed compositions in gene therapy. Further, the Office Action asserts that the specification does not provide any working examples of methods of gene therapy using the disclosed nucleotide sequences, and that successful implementation of gene therapy protocols had not been routinely obtained at the time the present invention was made. Applicants respectfully traverse the rejection.

The specification discloses experiments showing that the c-erg and C-11 genes functionally inhibit calcification of osteoblasts (see description at pages 25-26), as shown by Alizarin red staining (Figure 10) and von Kossa staining. According to MPEP 2164.02, if the art is such that a particular *in vitro* model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the Examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on the finding that *in vitro* data did not support *in vivo* applications). Since the initial burden is on the examiner to give reasons for lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or an *in vivo* animal model example. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739. 747 (Fed. Cir. 1985).

Applicants respectfully submit that the data in the specification showing that the c-erg and C-11 genes functionally inhibit calcification of osteoblasts would be considered

by one skilled in the art as correlating to the functional inhibition of cell calcification *in vivo*. As noted on page 14 of the specification, lines 7-11, by virtue of this cell-calcification inhibition, the pharmaceutical compositions of the present invention may be used to treat various diseases, including those in which pathological calcification causes ossification such as OPLL and osteoarthritis. Accordingly, the skilled artisan would know how to use the claimed pharmaceutical compositions based on the disclosure in the specification.

As evidence that osteoblasts are an acceptable *in vitro* model of cell calcification, Applicants have attached hereto three abstracts. According to the abstract by Gu *et al.* (Acta Pharmacol. Sin. (2002) 23(9): 808-12), "the phenotype of developmental sequence of skull-derived osteoblasts can reflect the maturation of osteoblasts *in vitro* [and] is a convenient model for the research of osteoblasts biology." Mineral deposition was assessed in this study using Von Kossa staining, as reported in the present specification. Similarly, Collignon and colleagues report that primary cell cultures allow one to understand osteoblastic function, and that "osteoblast phenotype cells having the capacity to differentiate and mineralize *in vitro* would be a model to study endocrine regulation of osteoblastic function in large mammals" (Arch. Physiol. Biochem. (1997) 105(2): 158-66). Ecsedi also reports the use of an osteoblast-enriched cell line as an *in vitro* model to find effective compounds that increase bone calcification (Agents Actions (1994) 41(1-2): 84-5).

Thus, given the state of the art, the skilled artisan reading the specification would immediately see that calcification of osteoblasts *in vitro* is a suitable model for identifying compounds that modulate the calcification process. Applicants' showing that

the erg and C-11 genes functionally inhibit calcification of osteoblasts *in vitro* is therefore significant evidence correlating to a use of these genes in pharmaceutical compositions for the treatment of diseases involving pathological calcification.

The Office Action further argues that successful implementation of gene therapy protocols had not been routinely obtained at the time the present invention was made. Applicants respectfully disagree. According to the specification, the pharmaceutical compositions of the invention may be delivered, for instance, by local injection, subcutaneous injection and oral administration (see page 14, lines 18-20). It was well known prior to the filing of this invention that direct injection of naked nucleic acids into the muscle or skeletal muscle results in high levels of expression of injected reporter genes, via uptake of the nucleic acids into cells in the vicinity. See, e.g., U.S. Patent 5,580,859 (issued December 3, 1996), enclosed herein. In contrast, none of the articles relied on by the examiner discuss local delivery applications. Given that all the parameters of delivering nucleic acids to mammalian cells by direct injection were worked out prior to the filing of the present invention, there is every reason to believe that local delivery of the claimed pharmaceutical compositions by direct injection could be done as disclosed in the specification. Thus, one skilled in the art and knowledgeable regarding the state of the art would know how to make and use the compositions of the claimed invention based on the guidance provided in the specification.

In view of the remarks provided above, reconsideration and withdrawal of the rejection of claims 32 and 34 under 35 U.S.C. §112, first paragraph, are respectfully requested.

Claims 36-38 were separately rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way so as to enable one skilled in the art to make and use the invention. Essentially, the Office Action asserts that it is impossible to use a primer for nucleotides 645-662 of SEQ ID No. 1 to amplify the polynucleotide encoding SEQ ID No. 4 since the primer sequence lacks nucleotides that are a part of SEQ ID No. 4. Applicants respectfully traverse the rejection as it pertains to claim 36 as amended above.

Claim 36 was amended above to more clearly point out that the claimed primer is capable of amplifying a nucleic acid encoding a protein comprising amino acids derived from SEQ ID NO: 4 wherein the derivation comprises deletion, substitution or insertion of at least one amino acid, wherein said derived protein has cell-calcification inhibitory activity and increases DNA synthesizing ability of cells. This option is intended to cover primers that amplify sequences encoding proteins encoded by SEQ ID No. 1 and like sequences (which may be derived from the gene encoding SEQ ID No. 4 by the deletion, substitution or insertion of one or more of the nucleotides from the sequence of nucleotides 655-735 of SEQ ID No. 3). Applicants believe that this amendment resolves the rejection of claims 36-38 under §112, first paragraph.

In view of the amendment to claim 36 and the remarks above, reconsideration and withdrawal of the rejection of claims 36-38 are respectfully requested.

B. Written Description Rejection

Claim 36 was also rejected under 35 U.S.C. §112, first paragraph, as containing subject matter that was not described in the specification so as to convey to one skilled in

the art that the Applicants were in possession of the claimed invention at the time of filing. Applicants respectfully traverse the rejection as it pertains to claim 36 amended above.

Claim 36 as amended above is directed to a nucleic acid which is complementary to at least a portion of a nucleic acid encoding a C-11 protein selected from the group consisting of (a) a nucleotide primer capable of amplifying a nucleic acid encoding a protein comprising the amino acids as set forth in SEQ ID NO:2; (b) a nucleotide primer capable of amplifying a nucleic acid encoding a protein comprising amino acids derived from SEQ ID NO: 4 comprising deletion, substitution or insertion of at least one amino acid, wherein said derived protein has cell-calcification inhibitory activity and increases DNA synthesizing ability of cells; and (c) a nucleotide probe capable of identifying a nucleic acid encoding a protein having cell calcification inhibitory activity, wherein said complementary nucleic acids (a), (b), and (c) comprise the complement of nucleotides that span the splice junction at nucleotide 655 of SEQ ID NO:1. Thus, claim 36 is directed to nucleic acid primers and probes that span the site of the excision in SEQ ID No. 2 as compared to SEQ ID No. 4, that may be used to identify a C-11 gene or derivative thereof.

The specification provides support for probes that are specific for C-11 or c-erg at page 6, lines 21-26, and further discloses the position of the excision in C-11 relative to the c-erg gene at page 9, lines 21-24. Given that both sequences are disclosed in their entirety in the specification, *i.e.*, C-11 as SEQ ID No. 1 and c-erg as SEQ ID No. 3, and given that the only difference between the two genes as disclosed at page 9, lines 21-24, is the excision of nucleotides 655-735 of the c-erg gene, the skilled artisan would

immediately see upon reading the specification that probes specific to C-11 as disclosed at page 6, lines 21-26, would include nucleotide sequences spanning this excision or splice junction, i.e. at position 655 of C-11. Reconsideration and withdrawal of the rejection of claim 36 for lack of written description is therefore respectfully requested.

This reply is fully responsive to the Office Action dated January 15, 2003. Therefore, a Notice of Allowance is next in order and is respectfully requested.

Except for issue fees payable under 37 CFR §1.18, the commissioner is hereby authorized by this paper to charge any additional fees during the pendency of this application including fees due under 37 CFR §1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 CFR §1.136(a)(3).

If the Examiner has any further questions relating to this Reply or to the application in general, she is respectfully requested to contact the undersigned by telephone so that allowance of the present application may be expedited.

Respectfully Submitted,
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